REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 2-26 are pending in the application. Claims 16-24 are withdrawn from consideration. Claim 25 has been amended in a manner that is supported throughout the disclosure and by the claim as previously presented. Accordingly, no new matter is added to the disclosure as a result of entering this amendment.

Claims 2-15, 25 and 26 stand variously rejected. Claims 6, 7, 15, and 26 are indicated as being free of the prior art of record, except with respect to the priority documents, for which applicants are grateful.

Reconsideration and allowance of the application is respectfully requested.

Interview Summary

The undersigned and Michael Schiff, agent for the licensee, thank Examiners Yaen and Nickol for the courtesy of a telephone interview conducted November 24, 2003. The rejections of the claims were discussed during the interview. Applicants also proposed filing an RCE and requesting to switch to the group of claims directed to a method of treatment. While Applicants are grateful to the Examiners for agreeing to this proposal and wish to preserve this option for future prosecution, Applicants have chosen to address the rejections of the instant claims in order to move these claims toward allowance.

Objections to the Specification

The specification was objected to for informalities, and particularly with respect to typographical errors on pages 10, 11, 15, 16, 19, 20 and 34. Applicants have reviewed these pages and, where apparent to Applicants, have amended the specification accordingly. Applicants respectfully request that if the Examiner is aware of further errors, that such be specifically identified in the next action.

Withdrawal of the objection to the specification is respectfully requested.

Obviousness-type double patenting

The Officer Action maintains the previous rejection of certain claims in this application

for obviousness-type double patenting with respect to U.S. Patent 6,203,787. Claims 6, 7, and 15 stand newly rejected for obviousness-type double patenting with respect to U.S. Patent 6,207,147.

Applicants respectfully disagree, for reasons already of record in this application with respect to the '787 patent. Nevertheless, to facilitate prosecution of this application, applicants hereby undertake to file a terminal disclaimer over these patents as appropriate, upon indication that this application is otherwise in condition for allowance.

Rejection over the Kohler reference

Claims 2-5, 8-12, and 25 stand rejected under 35 USC § 102(b) as being obvious [*sic*] over the publication by Kohler et al., Cancer Immunol. Immunother. 26:74, 1988. The Office Action indicates that the compositions taught in the publication are indistinguishable from the invention embodied in these claims.

Applicants respectfully disagree. In the Amendment filed March 1, 2003, base claim 25 was amended to require that the pharmaceutical composition be formulated for administration into *a solid tumor or the bed of a solid tumor*. The skilled reader will recognize that the cells will be concentrated to a suitable volume (a few mL) in order to be suitable for administering directly into the tumor or tumor bed, and stay present there long enough to have the immunogenic and therapeutic effect according to the description.

In contrast, the compositions taught in the Kohler reference contain 0.8 to 2.3 $\times$ 10^{10} cells (Table 1), and *are always given intravenously* (page 75 ff., "Treatment plan"). The skilled reader will recognize that, in order to be safely administered as an intravenous infusion, such a large number of lymphocytes would have to be given diluted in saline in a much larger volume (10 to 100 mL). In contrast, the claimed method typically involves concentrating cells in a comparatively much smaller volume so that, upon administration into a solid tumor or a bed or a solid tumor, the cells are maintained in proximity with tumor antigen. Accordingly, the formulation of the invention embodied in these claims distinguishes it from anything taught or suggested in the Kohler reference.

Base claim 25 has been amended in this Response in a manner that incorporates a further distinguishing feature. The lymphocytes in the Kohler composition are HLA-haploidentical to the patient (Title and Abstract). This is important to Kohler's therapy, because the administered

lymphocytes are designed to attack the tumor directly. Accordingly, the cells are taken from a haploidentical relative so as to provide as close a tissue match to the patient as possible. This allows the activated cells to circulate long enough to perform their intended role. Kohler et al. teach against the use of allogeneic cells (page 74, col. 2 ¶ 2) as being subject to rapid rejection or in danger of generating an undesirable graft versus host reaction.

In contrast, this invention uses stimulated cells from an alloactivated donor, placed directly into the tumor bed. Without intending to be limited by theory, the implanted cells are believed to recruit the host's own immune system to react against tumor antigen present at the site. The working examples illustrate the activation of cells taken from donors who are unrelated to the subjects being treated. Accordingly, the claimed invention is different and actually contrary to what is taught in the Kohler reference.

Claims 2, 3, 4, and 5 are further distinguished from what is taught by Kohler et al. because of additional cell populations that are present in the composition. Claims 2, 3, and 4 require that there be alloactivated cells present from a plurality of donors, which contrasts from Kohler's single haploidentical donor (the other cells in Kohler's composition are inactivated). Claim 5 requires that inactivated cells be present from the patient being treated, whereas the inactivated stimulator cells used in Kohler et al. are from unrelated donors (page 75, col. 2 ¶ 2).

For all these reasons, the claimed invention is patentable over the Kohler reference. Withdrawal of this rejection is respectfully requested.

Rejection over the Phillips reference

Claims 2, 8-13, and 25 stand rejected under 35 USC § 102(b) as being anticipated by the publication of Philips et al. (J. Exp. Med. 159:993, 1984). The Office Action indicates that an excipient is a design choice that does not render the "main component" of the product patentable.

Applicants respectfully disagree. The excipient is not referred to in the preamble of the claim, it is recited in the body of base claim 25 as a *required component* of the composition. The test under § 102 is whether all the required components of the claimed composition are taught in a single prior-art reference.

The Phillips publication is inadequate to sustain a § 102 rejection under this test. This is a study of natural killer cells prepared in tissue culture -- an academic study designed to make and characterize specialized leukocytes that can be prepared in vitro. There is no teaching in the

Phillips reference to use the activated cells in the manufacture of a pharmaceutical compound, or for any other clinical purpose. Thus, the pharmaceutical excipient of the invention claimed in this patent application is missing, and the reference does not anticipate the invention. Likewise, no rejection is possible under § 103 — there can be no motivation to change a pharmaceutical excipient as a "design choice", when there is no suggestion to use the cells of Phillips et al. in a pharmaceutical composition to begin with.

Withdrawal of this rejection is respectfully requested.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-005CIP.

Respectfully submitted,
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